Attorney Docket No.: 00.22US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Macs, et al.

Serial No.: 09/773,351 Group Art Unit: 1617

Filed: January 31, 2001 Examiner: Jiang, Shaojia A.

For: Cholesterol Sulfate and Amino Sugar Compositions for Enhancement of Stratum Corneum Function

RESPONSE PURSUANT TO 37 CFR 1.111

REMARKS

§112 Rejections

The Examiner has rejected Claims 1 and 3 to 20 for failing to reasonably convey to one skilled in the art that the inventor(s) possessed the claimed invention under §112, first paragraph. In particular, the phrase "integral with" is, according to the Examiner, new matter. Therefore, one of ordinary skill in the art could not ascertain and interpret what is encompassed by this phrase. However, Applicants respectfully traverse this rejection because the term is one which one of ordinary skill in the art would familiar. The term "integral with" has an ordinary meaning that is accessible in any dictionary, and the term is commonly used in the art. Further, the words used in the claims do not need to be found *ipsis verbis* in the specification to satisfy the written description requirement of §112. Rather, what is required is a reasonable conveyance to one of ordinary skill in the art that Applicants possessed the subject matter at issue. *In re Edwards* , 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978). Thus, what is to be questioned is whether the specification provides adequate direction which reasonably would lead one of ordinary skill in the art to the phrase "integral with." *Fujikawa v. Wattanasin,* 39 USPQ2d 1895 (CAFC 1996); *Id.* at 1352, 196 USPQ at 467.

The Examiner admits that "[t]he recitation 'integral with' could be interpreted as 'mixed with' or 'a mixture of' according [sic] its plain and ordinary meaning. Applicants fully agree with this interpretation and therefore assert that support for the amendment to the claims is found in the present specification which repeatedly refers to the present invention as a mixture. In the present specification, support is found for the amendments made in Applicants' Response of January 5, 2004 at page 4, lines 11 to 12, 21 to 29, and page 5, lines 26 to 28 for the phrase "integral with." The first is at page 4, lines 11 to 12 wherein the discovery of the present invention is described. Basically, the present invention finds that two opposing components do not cancel each other out in a composition even when the two components

are mixed together. Another reference in the specification is at page 4, lines 21 to 29 including lines 22 to 24 which were noted in Applicants' Response of January 5, 2004 as providing support for the amendment. The two components are noted therein as being in combination with one another. Further, the compositions containing this combination are referred to as a mixture.

The common definition of "mixture" is a combination of different elements (or components.) Thus, these two words are used interchangeably. The present invention is a mixture, and therefore, the whole composition of the present invention contains the two components, one integral with the other as based on the basic definition of "integral" which is to be of, pertaining to, or belonging as a part of the whole. The components of the mixture in the present invention are noted as being a part of a whole in the specification at page 5, lines 26 to 28. The components of the present invention are described as belonging to a whole. Specifically, at this point in the specification, formulations of the present invention are described as having a mixture of cholesterol sulfate and the exfoliant combined with other components. The present invention is described as a mixture throughout the specification. Thus, as the Examiner admits that one of ordinary skill in the art would understand that integral with can be interpreted as mixture according to its plain and ordinary meaning, Applicants assert that there is ample support in the specification for the amendments made in the Response of January 5, 2004. No new matter is added, and Applicants request that the rejection for new matter be withdrawn.

The §112 rejection is based on a failure, according to the Examiner, to particularly point out and distinctly claim the subject matter of the present invention. As indicated above, "integral with" is clearly defined in the specification. Therefore, contrary to the Examiner's assertion, one of ordinary skill in the art would know what the metes and bounds of the claims are. The phrase "integral with" merely describes a quality of what it means to be a mixture or a combination. Therefore, there is no broadening beyond the combination and mixture described by the claims, and indeed, the phrase provides further clarification to the mixture and combination of the present invention. The phrase "integral with" is a clarification to quell the Examiner's concern that there is any commonality between two components in a mixture, as in the present invention, and two components in a lipid vesicle, as in the cited prior art. There is no such connection between the two. Thus, the fact that the phrase "integral with" can be interpreted as "mixed with" or a "mixture" according to its plain and ordinary meaning does not render the claims indefinite. Rather, based on this factual situation it renders the claims more definite because the present invention is a mixture and the phrase "integral with" offers more clarification of what it means to be a mixture. This fact is being disregarded in the present rejection under §112 and in the rejections which are discussed further below. With respect to the rejection under §112, second paragraph, Applicants request that it be withdrawn.

II. Novelty and Obviousness Rejections

The Examiner has rejected Claims 1 and 3 to 20 provisionally under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-21 of copending Application No. 10/424,616. The claims of the copending Application are believed to be still pending. Applicants acknowledge the provisional double patent rejection made by the Examiner. However, in light of the arguments set forth below, Applicants will make a terminal disclaimer, if necessary, in the event that allowable subject matter is indicated.

A. U.S. Patent No. 5,650,166 ("the '166 Ribier reference")

In the present office action, the Examiner finds that Claims 1 and 3 to 9 are anticipated by the '166 Ribier reference. The Examiner asserts that the '166 Ribier reference discloses a composition comprising cholesterol sulfate and N-acetylglucosamine. However, Applicants have argued repeatedly, without comment from the Examiner on this point, that the elements in the '166 Ribier reference are not arranged as they are in the present invention. The arrangement in the '166 Ribier reference is not a "mixture" as one of ordinary skill in the art would understand it. Two ingredients that are separated from one another, as they are in the '166 Ribier by virtue of the vesicle formation, cannot be a mixture or be integral with one another because they are not actually combined. The Examiner has admitted in the present office action that a mixture can be interpreted by one of ordinary skill in the art as being integral with. There is no integration where there is separation. To anticipate under §102(b), a single prior source must contain all the essential elements of the anticipated claim. *Lindemann Maschinenfabrik v. American Hoist and Derrick*, 730 F.2d 1452, 1458, 221 USPQ 481, 485-86 (Fed. Cir. 1984); *Shanklin Corp. v. Springfield Photo Mount Co.*, 521 F.2d 609, 187 USPQ 129 (1st Cir. 1975). Therefore, the '166 Ribier reference does not anticipate the claims of the present invention because it fails to contain the essential element of the present invention of being a mixture or, in other words, integral with. Applicants request that the rejection of the claims based on anticipation be withdrawn.

The Examiner notes in the office action that the present claims are not limited to specific steps in a method. However, this is not necessary as the limitations of the claims sufficiently describe an integral mixture of components which one of ordinary skill in the art would recognize as being distinct and separate from the same components physically located in separate bilayers of a liposome (or vesicle). This has not been addressed by the Examiner. "A proper analysis under §103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2)

whether the prior art would also have revealed that in so making or carrying out [the claimed process], those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 20 USPQ2d 1438, 1442 (CAFC 1991); see *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). These two factors have not been met in the present case. First, there is no teaching or suggestion in the prior to make a mixture of the pertinent components in the '166 Ribier reference. The teaching in the '166 Ribier reference of the components physically located in separate bilayers of a liposome is contrary and opposite to the mixture of the same components of the present invention. In a mixture, the components are not separated; but rather, are integrated. Since the '166 Ribier reference only teaches the components in a state of separation, the mixture of the present invention is not taught or suggested by the '166 Ribier reference.

The second factor of an obviousness analysis is likewise not met because the '166 Ribier reference fails to reveal that making the composition of the present invention, namely the mixture of the components, would be expected by one of ordinary skill in the art to have reasonable success. This factor is linked to the first factor because as long as there is no teaching or suggestion in the '166 Ribier reference to make the mixture of the present invention, there likewise, cannot be a reasonable expectation of success to do what is not taught or suggested. But beyond this, the teachings of the '166 Ribier reference are aimed at treating two different layers of the skin at the same time. Thus, the components of the '166 Ribier compositions start out separated in the composition and the components remain separated as they are directed to two different areas of the skin. There is never a mixing or integration of the components of the '166 Ribier compositions. This is illustrated by the teaching at column 1, lines 11 to 14, where the '166 Ribier compositions are described as comprising at least one active agent conveyed via at least two distinct types of lipid vesicles. Additional support is found at column 2, lines 19 to 21, of the '166 Ribier reference wherein it is taught that the alleged invention involves two different agents to act in different areas of the skin. The different agents act in different areas due to the different lipid vesicles containing them. The different vesicles are classified based on the different types of action (see column 2, lines 34 to 41.) Every aspect of the '166 Ribier compositions relates to being separate and distinct.

Not only do the components of the '166 Ribier compositions exist separately in the composition; but, they are further targeted to act in separate and distinct areas of the skin transported by separately classified lipid vesicles. The two components of the '166 Ribier reference are intended to be separate and distinct at all times (i.e., not mixed, combined, nor integrated at any time.) Thus, the '166 Ribier reference does not teach, suggest, nor motivate one of ordinary skill in the art to make the compositions

of the present invention having mixed components. Accordingly, the present invention is not obvious in view of the '166 Ribier reference and Applicants request that this rejection be withdrawn.

B. U.S. Patent Nos. 5,925,364 and 5,411,742

In the present office action, the Examiner rejects Claims 1 and 3 to 20 because both cited references, U.S. Patent Nos. 5,925,364 ("the '364 reference") and 5,411,742 ("the '742 reference"), teach an integral mixture in a stabilized oil-in-water emulsion without discrete layers of a lipid vesicle. The Examiner notes that the preparation of the vesicles involves a mixing step in which the final product, an oil-in-water emulsion is formed without discrete layers of a lipid vesicle. However, the Examiner's description of the preparation at column 6 to 7 of the '364 reference is not accurate because indeed what is formed are discrete layers of a lipid vesicle. This is supported by the teachings of another cited reference, the '742 reference. Specifically, it is indicated in the '742 reference at column 1, lines 38 to 54, that ionic lipids are capable of swelling in an aqueous solution to form a lamellar phase, and after stirring, to form vesicles dispersed in the aqueous solution. Thus, the formation of discrete layers of a lipid vesicle is precisely what occurs when the ionic lipid is mixed in the '364 preparation. The '364 preparation does not produce a mixture because the ionic lipids swell under the action of mixing to form discrete layers of a lipid vesicle which separates its contents from the other ingredients in the composition, namely the outside media (e.g., the aqueous phase).

There is a stark contrast between the act of mixing and the act of producing a mixture. In none of the cited references does the act of mixing produce a mixture. To the contrary, the act of mixing causes the ionic lipid to swell and arrange itself in an orderly manner to form discrete layers of a vesicle dispersed in the aqueous phase. Thus, the ionic lipid used with other materials to make the vesicle is not mixed with the content of the aqueous phase; but, rather is used to form a discrete entities present in the outside media (i.e., the aqueous phase). They are not mixed. As previously discussed, the vesicle holds active agents within and keeps the actives separate from media outside of its walls. Creating a vesicle is akin to encapsulation where the actives inside and the materials used to encapsulate are not mixed with the outside media. Therefore, the combination of the '364 Ribier reference and the '742 reference fails to teach or suggest the mixture of the present invention.

Applicants also point out teachings in each of the cited references indicating that the compositions contain vesicles. First, Applicants direct the Examiner's attention to the abstract of the '364 reference wherein it is stated "[oily globules are] provided with a lamellar liquid crystal coating and are dispersed in an aqueous phase." This is reiterated at column 2, lines 24 to 33, providing further detail about the coating. Specifically, it is noted therein that each oily globule is obtained from a lipophilic

surfactant, a hydrophilic surfactant, and an ionic amphiphilic lipid (the ionic lipid previously noted as swelling and forming vesicles). Further, the "coated oily globules" have a diameter less than 500 nanometers. Thus, as Applicants have asserted the oil globules in the '364 reference are coated and as such they resemble lipid vesicles because the active inside the oil globules is separated from the aqueous phase and the contents of the aqueous phase.

The lipid vesicle type component of the '364 reference is also described at column 2, lines 52 to 63. The '364 emulsions are described as having fatty phase droplets that are extremely small in size and most importantly, that are coated with an extremely fine oligolamellar layer. Thus the contents of the coated oily droplets are separated from the contents of the aqueous phase. One of ordinary skill in the art would also understand that the coated oily globules of the '364 reference are similar to lipid vesicles because at column 2, lines 64 to 67, the ability to transport and deliver active agents contained in the coated oily globule is taught. Previously, Applicants asserted that the oily globules coated with a lamellar liquid crystal coating in the '364 Ribier reference are similar to the lipid vesicles of the '166 Ribier reference. Specifically, the '364 Ribier reference discloses an emulsion composition that has oily globules with a lamellar liquid crystal coating dispersed in an aqueous phase. Like that of the '166 Ribier reference, the '364 compositions can include materials such as alkali metal salts of cholesteryl sulphate as the ionic amphiphilic lipid, taught as one of components of the coating (i.e., similar to the membrane layers of the '166 Ribier vesicles). However, the teaching of the '364 reference to include an alkali metal salt of cholesteryl sulfate as part of the coating of an oily globule is not a teaching or suggestion to make a mixture of cholesterol sulfate with any other component as it is described in the present invention. Therefore, the '364 Ribier reference, like that of the '166 Ribier reference, fails to teach or suggest the integral mixture of the exfoliant and cholesterol sulfate in the present invention.

According to the Examiner, the '364 Ribier reference in combination with the '742 reference is obvious to one of ordinary skill in the art. Both the '364 Ribier reference, as shown above, and the '742 reference disclose lipid vesicle/lamellar systems. Specifically, it is indicated in the '742 reference at column 1, lines 38 to 54, that ionic lipids are capable of swelling in an aqueous solution to form a lamellar phase, and after stirring, to form vesicles dispersed in the aqueous solution. The amphiphilic lipids capable of forming vesicles noted in the '742 reference include, *inter alia*, ionic amphiphilic lipids (note these are the same ionic amphiphilic lipids disclosed in the '364 Ribier reference at column 3, line 43, and the '166 Ribier reference at column 3, lines 45 to 47, both of which discloses vesicles.) Thus it can clearly be seen from the descriptions in both the '364 Ribier reference and the '742 reference that these the alleged inventions both relate to lipid vesicles/lamellar systems like that of the '166 Ribier

reference. Therefore, the combination of these references for reasons stated above, fail to teach or suggest an integral mixture of exfoliant and cholesterol sulfate as in the present invention.

Finally, even if the interpretation of one of ordinary skill in the art were that a lipid vesicle containing cholesterol sulfate in the membrane layer and NADG encapsulated therein was equivalent to the integral mixture of the present invention, Applicants assert that it would be rebutted by the surprising results of the present invention. The Examiner previously noted in the Advisory Action and the Final Office Action that the Example in the present specification does not provide clear and convincing evidence of nonobviousness or unexpected results over the cited prior art because there is no direct comparison of the same. However, as Applicants have pointed out in the present response, the two systems are not the same and there is no reason to believe that the integral mixture of the ingredients of the present invention directly in a vehicle would necessitate a comparison with a lipid vesicle as these are two completely different systems and different arrangements of the components. To support this fact, Applicants submit herewith a copy of an article, Bouwstra et al., "Cholesterol sulfate and calcium affect stratum corneum lipid organization over a wide temperature range" Journal of Lipid Research, vol. 40, 2303-3212 (Dec. 1999). In the article, the authors note that reduced levels of cholesterol sulfate contribute to desquamation, thus indicating that the presence of cholesterol sulfate would maintain the integrity of the stratum corneum and prevent desquamation. This has not been addressed. Therefore, Applicants maintain that one of ordinary skill in the art would expect a combination of cholesterol sulfate and an exfoliant to have no effect on the surface on the skin because while the exfoliant would contribute to desquamation, the cholesterol sulfate would act to prevent desquamation.

The present invention is based on the finding that two ingredients, the cholesterol sulfate and the exfoliant, although they have opposing activities, when added as a mixture to a pharmaceutical or cosmetic vehicle, do not neutralize one another's activities, but rather their activity occurs in tandem, and can improve or maintain a healthy skin barrier. This benefit cannot even be addressed with the cited references because these two materials form lipid vesicles, and therefore, are not in fact mixed. Rather, they are separated such that one, the cholesterol sulfate, is part of a protective membrane that encases the other, the NADG. The whole point of the lipid vesicles/lamellar systems of the cited references is to protect and prevent the active inside from integrating with anything else. Thus, a comparison of this kind would be futile. Finally, Applicants point out that the burden to provide evidence of unexpected results does not pass from the Examiner to Applicants until a *prima facie* case of obviousness has been made.

CONCLUSION

The present invention, as amended, is an integral mixture of an exfoliant and a cholesterol sulfate that is not taught or suggested by the cited references describing lipid vesicles having one bilayer containing N-acetyl D-glucosamine, and another bilayer containing cholesterol sulfate as the component are arranged differently. Because none of the cited references alone nor in combination would lead one of ordinary skill in the art to the compositions and methods of the present invention, a *prima facie* case of obviousness has not been established. Applicants request therefore, that the Examiner's rejection under §103 be withdrawn. In view of the arguments presented above in the present submission, the claims are believed to be in condition for allowance, and issuance of a Notice of Allowance is respectfully solicited.

Respectfully submitted,

Date June 23, 2004

Dorene M. Price (Reg. No. 43,018)
Estee Lauder Companies
125 Pinelawn Road
Melville, NY 11747
(631) 531-1194